CLAIMS

What is claimed is:

1. An isolated nucleic acid molecule encoding a humanized immunoglobulin light chain or antigen-binding fragment thereof comprising CDR1, CDR2 and CDR3 of the light chain of murine 1D9 antibody and a human light chain framework region.

2. The isolated nucleic acid molecule of Claim 1, wherein the human framework region is derived from the light chain of the human HF-21/28 antibody.

3. The isolated nucleic acid molecule of Claim 2, wherein said humanized immunoglobulin light chain or antigen-binding fragment thereof comprises the variable region of SEQ ID NO: 9.

4. The isolated nucleic acid molecule of Claim 3, wherein said nucleic acid molecule comprises the variable region coding sequence of SEQ ID NO: 95.

5. An isolated nucleic acid molecule encoding a humanized immunoglobulin heavy chain or antigen-binding fragment thereof comprising CDR1, CDR2 and CDR3 of the heavy chain of the 1D9 antibody and a human heavy chain framework region.

6. The isolated nucleic acid molecule of Claim 5, wherein the human framework region is derived from the heavy chain of the human 4B4'CL antibody.

7. The isolated nucleic acid molecule of Claim 6, wherein the humanized immunoglobulin heavy chain or antigen-binding fragment thereof comprises the variable region of SEQ ID NO: 10.

8. The isolated nucleic acid molecule of Claim 7, wherein said nucleic acid molecule comprises the variable region coding sequence of SEQ ID NO: 96.

9. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a humanized immunoglobulin light chain or antigen-binding fragment thereof, said light chain or antigen-binding fragment thereof having an amino acid sequence comprising at least a functional portion of the light chain variable region amino acid sequence of SEQ ID NO: 9.

10. The isolated nucleic acid molecule of Claim 9 comprising the variable region coding sequence of SEQ ID NO: 95.

11. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the humanized immunoglobulin heavy chain or antigen-binding fragment thereof, said heavy chain or antigen-binding fragment thereof having an amino acid sequence comprising at least a functional portion of the heavy chain variable region amino acid sequence of SEQ ID NO: 10.

12. The isolated nucleic acid molecule of Claim 11 comprising the variable region coding sequence of SEQ ID NO: 96.

13. An expression vector comprising a fused gene encoding a humanized immunoglobulin light chain, said gene comprising a nucleotide sequence encoding a CDR derived from a light chain of a nonhuman antibody having

binding specificity for CCR2 and a framework region derived from a light chain of human origin.

14. The expression vector of Claim 13, wherein the nonhuman antibody is murine antibody 1D9.

15. A host cell comprising the expression vector of Claim 13.

16. An expression vector comprising a fused gene encoding a humanized immunoglobulin heavy chain, said gene comprising a nucleotide sequence encoding a CDR derived from a heavy chain of a nonhuman antibody having binding specificity for CCR2 and a framework region derived from a heavy chain of human origin.

17. The expression vector of Claim 16, wherein the nonhuman antibody is murine antibody 1D9.

18. A host cell comprising the expression vector of Claim 16.

19. A host cell comprising a first recombinant nucleic acid molecule encoding a humanized immunoglobulin light chain and a second recombinant nucleic acid molecule encoding a humanized immunoglobulin heavy chain, wherein said first nucleic acid molecule comprises a nucleotide sequence encoding a CDR derived from the light chain of murine antibody 1D9 and a framework region derived from a light chain of human origin, and wherein said second nucleic acid molecule comprises a nucleotide sequence encoding a CDR derived from the heavy chain of murine antibody 1D9 and a framework region derived from a heavy chain of human origin.

20. A method of preparing a humanized immunoglobulin comprising maintaining a host cell of Claim 19 under conditions appropriate for expression of a humanized immunoglobulin, whereby humanized immunoglobulin chains are expressed and a humanized immunoglobulin is produced.

21. The method of Claim 20 further comprising the step of isolating the humanized immunoglobulin.

22. A fused gene encoding a humanized immunoglobulin light or heavy chain comprising:

a) a first nucleic acid sequence encoding an antigen binding region derived from murine monoclonal antibody 1D9; and

b) a second nucleic acid sequence encoding at least a portion of a constant region of an immunoglobulin of human origin.

23. A method of inhibiting the interaction of a cell expressing CCR2 with a ligand of CCR2, comprising contacting said cell with an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

24. A method according to Claim 23 wherein the cell is selected from the group consisting of lymphocytes, monocytes, granulocytes, T cells, basophils, and cells comprising a recombinant nucleic acid encoding CCR2 or a portion thereof.

25. A method according to Claim 23 wherein the ligand is a chemokine.

26. A method according to Claim 25 wherein the chemokine is selected from the group consisting of MCP-1, MCP-2, MCP-3, MCP-4 and combinations thereof.

27. A method according to Claim 23 wherein the ligand is HIV.

28. A method of inhibiting HIV infection of a cell, comprising contacting a cell with an effective amount of a composition comprising a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

29. A method of treating HIV in a patient comprising administering to the patient a composition comprising an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

30. A method of inhibiting HIV infection in a patient, comprising administering to the patient a composition comprising an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

31. A method of inhibiting a function associated with binding of a chemokine to mammalian CCR2, comprising contacting CCR2 with an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen

binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin, wherein said humanized immunoglobulin inhibits binding of said chemokine to mammalian CCR2 and inhibits one or more functions associated with binding of the chemokine to CCR2.

32. A method according to Claim 31 wherein the chemokine is selected from the group consisting of MCP-1, MCP-2, MCP-3, MCP-4 and combinations thereof.

33. A method of inhibiting leukocyte trafficking in a patient, comprising administering to the patient a composition comprising an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin which binds to mammalian CCR2 or portion of CCR2 and inhibits binding of a ligand to the receptor.

34. A method according to Claim 33 wherein the ligand is a chemokine.

35. A method according to Claim 34 wherein the chemokine is selected from the group consisting of MCP-1, MCP-2, MCP-3, MCP-4 and combinations of the foregoing.

36. A method of treating a CCR2-mediated disorder in a patient, comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

37. A method according to Claim 36 wherein the disorder is an inflammatory disorder.

38. A method of inhibiting restenosis in a patient, comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

39. A humanized immunoglobulin light chain or antigen-binding fragment thereof having binding specificity for CCR2 comprising an amino acid sequence selected from the group consisting of:

a) SEQ ID NO: 12;

b) SEQ ID NO: 13;

c) SEQ ID NO: 14; and

d) SEQ ID NO: 15.

40. A humanized immunoglobulin heavy chain or antigen-binding fragment thereof having binding specificity for CCR2 comprising an amino acid sequence selected from the group consisting of:

a) SEQ ID NO: 17;

b) SEQ ID NO: 18;

c) SEQ ID NO: 19; and

d) SEQ ID NO: 20.

41. A humanized immunoglobulin light chain or antigen-binding fragment thereof having binding specificity for CCR2 encoded by a nucleic acid molecule comprising SEQ ID NO: 98.

42. A humanized immunoglobulin heavy chain or antigen-binding fragment thereof having binding specificity for CCR2 encoded by a nucleic acid molecule comprising SEQ ID NO: 97.

43. A method according to Claim 38, wherein said restenosis is associated with vascular intervention in said mammal.

44. A method according to Claim 43, wherein said vascular intervention comprises angioplasty.

45. A method according to Claim 43, wherein said vascular intervention comprises stent placement.

46. A method according to Claim 43, wherein said vascular intervention comprises angioplasty and stent placement.

47. A method of inhibiting narrowing of the lumen of a vessel in a mammal, comprising administering to said mammal an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

48. A method of inhibiting neointimal hyperplasia of a vessel in a mammal, comprising administering to said mammal an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2, said immunoglobulin or fragment comprising an antigen binding

region of nonhuman origin and at least a portion of an immunoglobulin of human origin.

49. A method according to Claim 48, wherein said neointimal hyperplasia is associated with vascular intervention in said mammal.

50. A method according to Claim 49, wherein said vascular intervention comprises angioplasty.

51. A method according to Claim 49, wherein said vascular intervention comprises stent placement.

52. A method according to Claim 49, wherein said vascular intervention comprises angioplasty and stent placement.

53. A method according to Claim 36, wherein said CCR2-mediated disorder is an autoimmune disorder.

54. A method according to Claim 53, wherein the autoimmune disorder is selected from the group consisting of multiple sclerosis and rheumatoid arthritis.

55. A method according to Claim 54 wherein the autoimmune disorder is multiple sclerosis.

56. A method according to Claim 36, wherein the CCR2-mediated disorder is selected from the group consisting of atherogenesis and atherosclerosis.

57. A humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a light chain and a complementary heavy chain, wherein said light chain comprises a variable region comprising SEQ ID NO: 12.

58. A humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a complementary light chain, wherein said heavy chain comprises a variable region comprising SEQ ID NO: 17.

59. A humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a light chain, wherein said light chain comprises a variable region comprising SEQ ID NO: 12, and wherein said heavy chain comprises a variable region comprising SEQ ID NO: 17.

60. A method of inhibiting the interaction of a cell expressing CCR2 with a ligand of CCR2, comprising contacting said cell with an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a light chain, wherein said light chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL.

61. A method of inhibiting HIV infection in a patient, comprising administering to the patient a composition comprising an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a light chain, wherein said light chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL.

62. A method of inhibiting a function associated with binding of a chemokine to mammalian CCR2, comprising contacting CCR2 with an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a light chain, wherein said light chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL, wherein said humanized immunoglobulin inhibits binding of said chemokine to mammalian CCR2 and inhibits one or more functions associated with binding of the chemokine to CCR2.

63. A method of treating a CCR2-mediated disorder in a patient, comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a light chain, wherein said light chain

comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL.

64. A method of inhibiting restenosis in a patient, comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2 comprising a heavy chain and a light chain, wherein said light chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain comprises at least one complementarity determining region derived from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL.

65. A humanized immunoglobulin light chain or antigen-binding fragment thereof having binding specificity for CCR2 comprising the amino acid sequence of SEQ ID NO: 107.